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AOGS REVIEW ARTICLE

Cerclage for short cervix in twin pregnancies: systematic review and meta-analysis of randomized trials using individual patient-level data

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Key words
Preterm birth, cerclage, twins, cervical length, meta-analysis

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Conflict of interest
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Abstract

Objective. To evaluate the efficacy of cerclage for preventing preterm birth in twin pregnancies with a short cervical length. *Design.* We performed an individual patient data meta-analysis. Searches were performed in electronic databases. *Setting.* Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA. *Population.* Twin pregnancies in mothers with short cervical length. *Methods.* We performed an individual patient data meta-analysis of randomized trials of twin pregnancies screened by transvaginal ultrasound in second trimester and where mothers had a short cervical length <25 mm before 24 weeks. Eligible women had to be randomized to cerclage vs. no-cerclage (control). *Main outcome measures.* The primary outcome was preterm birth <34 weeks. *Results.* Three trials with 49 twin gestations with a short cervical length were identified. All original databases for each included trial were obtained from the primary authors. Risk factors were similar in the cerclage and control groups, except that previous preterm birth was more frequent and gestational age at randomization and delivery were earlier in the cerclage group compared with the control group. Adjusting for previous preterm birth and gestational age at randomization, there were no statistically significant differences in primary (adjusted odds ratio 1.17, 95% confidence interval 0.23–3.79) and secondary outcomes. Rates of very low birthweight and of respiratory distress syndrome were significantly higher in the cerclage group than in the control group. *Conclusion.* Based on these Level 1 data, cerclage cannot currently be recommended for clinical use in twin pregnancies with a maternal short cervical length in the second trimester. Large trials are still necessary.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CL, cervical length; GA, gestational age; NICU, neonatal intensive care unit; PTB, preterm birth; RCTs, randomized controlled trials; RR, relative risk; TVU, transvaginal ultrasound.

Key Message

Cerclage does not prevent preterm birth in asymptomatic twin gestations with a maternal short cervical length on transvaginal ultrasound.

Introduction

The incidence of twin gestations has increased, mostly because of increased use of assisted reproductive technol-

ogies (1). Twin pregnancies are at increased risk of preterm birth (PTB), which is the primary reason for their increased morbidity and mortality compared with singleton pregnancies. Twins account for about 3% of all pregnancies in the USA, but constitute at least 10% of cases of PTB (2), over 30% of very low birthweight infants, and are associated with nearly 20% of infant mortality (3).

A short cervical length (CL) on transvaginal ultrasound (TVU) has been shown to be a good predictor of PTB, including twin pregnancies (4). In singleton pregnancies with a previous PTB and a short CL < 25 mm before 24 weeks of gestation, cerclage was associated with significant decreases in PTB and perinatal morbidity and mortality in a meta-analysis of randomized controlled trials (RCTs) (5). In contrast, the effect of cerclage in twins with a short CL < 25 mm has been insufficiently studied, with meta-analysis data showing a possible harm from cerclage compared with controls (6).

The aim of this meta-analysis was to systematically review all RCTs on cerclage for prevention of PTB in women with asymptomatic twin gestations with a short TVU CL, assessing possible confounders in demographic characteristics, risk factors and subgroups for effects on the incidence of PTB.

Material and methods

Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to "cerclage," "cervical cerclage," "short cervix," "ultrasound" and "randomized trials" from 1966 until September 2014. No restrictions for language or geographic location were applied. We did not exclude any trials based on their publication status or language. This review strategy has been cited to capture up to 97% of relevant literature (7). We included RCTs of asymptomatic twin gestations screened by TVU in the second trimester of pregnancy and where the mothers were found to have a short CL < 25 mm. Eligible women were randomized to cerclage vs. no cerclage (control group). Exclusion criteria were quasi-randomized trials, history-indicated cerclage, twin-only-indicated cerclage, physical examination-indicated cerclage and major fetal anomaly. For this the individual patient data meta-analysis encompassed all original databases for each included RCT as obtained from the primary authors.

The primary outcome was predefined as PTB < 34 weeks of gestation. Secondary outcomes included PTB < 37 weeks, PTB < 35 weeks, PTB < 32 weeks, PTB < 28 weeks, PTB < 24 weeks, perinatal death, low birthweight (defined as <2500 g), very low birthweight (defined as <1500 g), respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and neonatal intensive care unit (NICU) admission.

We planned subgroup analyses in twin gestations with previous PTB; twins without previous PTB; twins with previous second trimester loss and twins with cone biopsy. We planned to stratify results by gestational age at detection of the short CL. We also planned to examine the effect limiting the analysis to women with CL ≤ 15 mm.

Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42014013577) (8).

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk" of bias (9).

The data analysis was completed independently by the authors (GS, VB) using Review Manager 5.3 (Cochrane, London, UK). The completed analyses were then compared and any difference was resolved with review of the entire data and independent analysis. The random effects model of DerSimonian and Laird was used to obtain the pooled risk ratios estimate. Pooled estimates were based on the crude risk ratio. A logistic regression was performed to correct data for those variables significantly different between groups. Results of the logistic analysis are presented as adjusted odds ratio (aOR) with 95% confidence interval (95% CI). The logistic regression was conducted using the Statistical Package for Social Science (SPSS) software, Version 20.0 (SPSS Inc., Chicago, IL, USA). The meta-analysis was performed following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (10). There was no funding source.

Results

Eighteen randomized trials of cerclage in pregnancy were identified (11–28). Fourteen were excluded because twin gestations were not evaluated (11–17,22–28), and one was excluded because it evaluated only history-indicated cerclage (18). All three trials that included twin mothers with short CL randomized to cerclage or control met the criteria for inclusion in this meta-analysis and so were analyzed (19–21). No similar systematic reviews were found during the search process. Figure 1 shows the flow diagram of studies identified in the systematic review (PRISMA template).

The risk of bias according to the Cochrane risk of bias tool is shown in Figure 2. All studies had both adequate random sequence generation and concealment allocation. Incomplete outcome data and selective reporting were

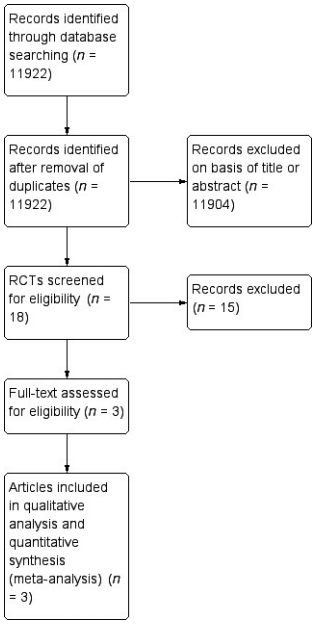

Figure 1. Flow diagram of studies identified in the systematic review (PRISMA template).

considered as having low risk of bias for all the studies (Figure 2).

Pooled descriptive data are presented in Table 1. Of the 49 twin gestations included in the three trials (19–21), 24 (49%) were randomized to cerclage, with 25 (51%) randomized to the control groups (no cerclage). Maternal characteristics were similar in the two groups except for the rate of previous PTB, which was higher in the cerclage group (25% vs. 4%, $p = 0.049$), and gestational age at randomization, which was earlier in the cerclage group (21.46 weeks vs. 23.32 weeks, $p = 0.019$) (Table 1). The gestational age at delivery was earlier in the cerclage group (30.33 vs. 34.20 weeks, $p = 0.007$), but there was no significant difference in latency from randomization to delivery (8.8 vs. 10.9 weeks, $p = 0.131$). A Forest plot of PTB < 34 weeks of gestation is shown in Figure 3.

Table 1. Descriptive data and selected outcomes for included twin pregnancies.

Variables	Cerclage (n = 24)	Control (n = 25)	p-value
Maternal age (years), mean ± SD	28.88 ± 5.40	28.08 ± 6.35	0.640
Race, African-American	4 (16.7)	0 (0)	0.500
Previous PTB <37 weeks	6 (25.0)	1 (4.0)	0.049
Previous STL (16–23 weeks)	3 (12.5)	0 (0)	0.110
Müllerian anomalies	0 (0)	0 (0)	–
Cone biopsy	2 (8.3)	4 (16.0)	0.667
Smoking	2 (8.3)	8 (32.0)	0.074
CL (cm) mean ± SD	18.6 ± 6.1	18.3 ± 4.7	0.817
GA at randomization (weeks), mean ± SD	21.4 ± 3.1	23.3 ± 2.1	0.019

Data are presented as number (percentage).
CL, cervical length; GA, gestational age; PTB, preterm birth; SD, standard deviation; STL, second-trimester loss.

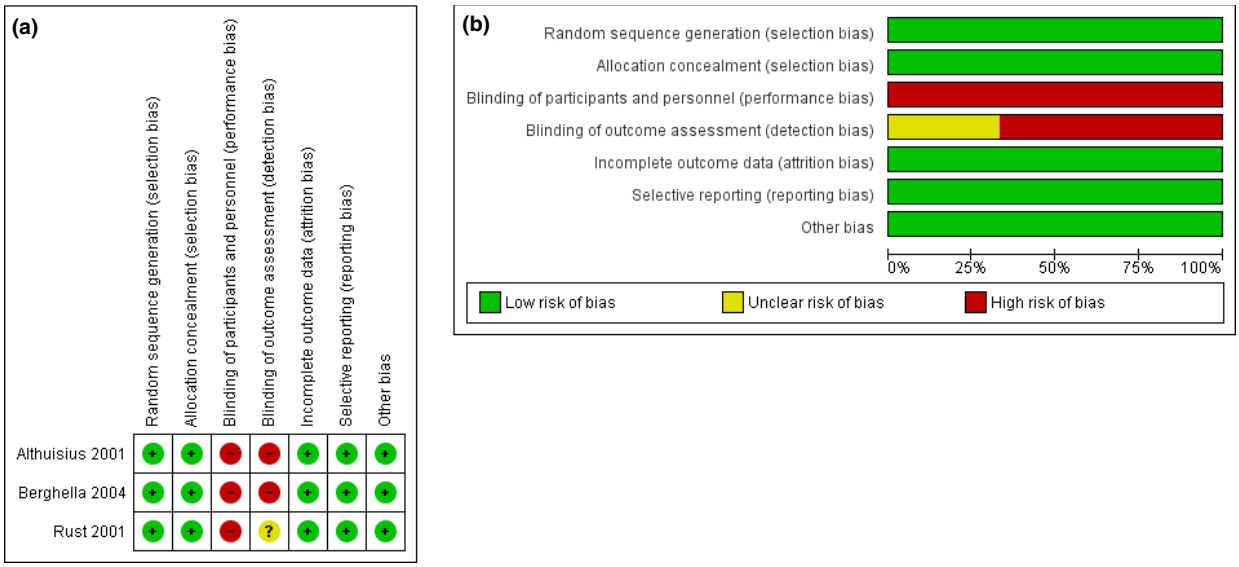

Figure 2. Assessment of risk of bias. (a) Summary of risk of bias for each trial; +, low risk of bias; –, high risk of bias; ?, unclear risk of bias. (b) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

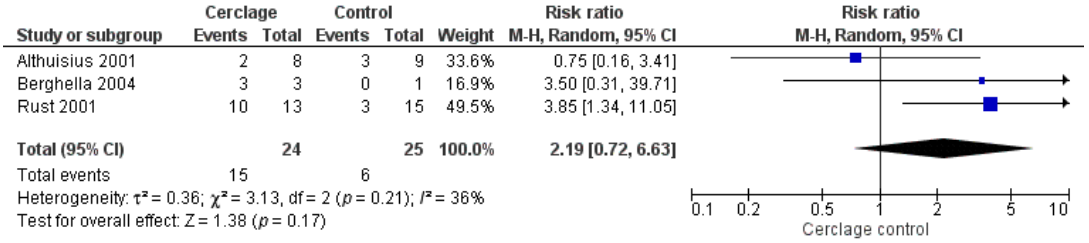

Figure 3. Meta-analysis of cerclage in twins and preterm birth at <34 weeks of gestation.

Adjusting for confounders (previous PTB and gestational age at randomization), women who received cerclage had a similar rate of PTB < 34 weeks compared with the control group (62.5% vs. 24.0%; aOR 1.17, 95% CI 0.23–3.79) (Table 2). Most secondary outcomes, including PTB < 37 weeks, PTB < 35 weeks, PTB < 32 weeks, PTB < 28 weeks, PTB < 24 weeks, perinatal deaths, intraventricular hemorrhage, sepsis and NICU admission were similar in the two groups. Very low birthweight (aOR 2.22, 95% CI 1.07–5.73) and respiratory distress syndrome (aOR 3.88, 95% CI 1.09–21.03) were more frequent in the cerclage group, though with borderline significance. No data were available on necrotizing enterocolitis (Table 2). There were no significant differences for PTB < 34 weeks in the subgroup analyses, once adjusted for confounders (Table 3).

Discussion

This meta-analysis of pooled data of the three RCTs evaluating the efficacy of cerclage in asymptomatic twin gestations screened by TVU in the second trimester of pregnancy and found to have a short CL < 25 mm, shows that cerclage is not associated with prevention of PTB compared with control women who do not receive a cerclage suture. Women who had cerclage were randomized about 2 weeks earlier, and delivered about 4 weeks earlier than the controls. We found no significant difference in the latency from randomization to delivery. Regarding neonatal outcomes, women who received cerclage had the same rate of perinatal deaths, low birthweight, intraventricular hemorrhage, NICU admission and sepsis, compared with the control group. The rate of very low birthweight and of respiratory distress syndrome was higher in the cerclage group compared with the controls. In the subgroup analyses we found no benefit or detriment of cerclage in this population. Results for these outcomes need to be interpreted with caution because of the small numbers.

In our 2005 meta-analysis we reported on data available at that time regarding ultrasound-indicated cerclage, focusing mostly on singleton gestations, and on the

Table 2. Primary and secondary outcomes in all twin pregnancies.

	Cerclage (n = 24)		Control (n = 25)			
Outcome	n	%	n	%	RR (95% CI)	aOR (95% CI)
PTB < 37 weeks	22	91.7	19	76.0	1.18 (0.91–1.53)	1.13 (0.17–8.66)
PTB < 35 weeks	18	75.0	9	36.0	1.63 (0.88–3.02)	1.44 (0.66–7.11)
PTB < 34 weeks	15	62.5	6	24.0	2.19 (0.72–6.63)	1.17 (0.23–3.79)
PTB < 32 weeks	11	45.8	4	16.0	2.48 (0.96–6.37)	1.77 (0.88–3.39)
PTB < 28 weeks	7	29.2	2	8.0	2.62 (0.72–9.51)	1.66 (0.62–4.01)
PTB < 24 weeks	5	20.8	0	0	N/A	N/A
Perinatal deaths	11/48	22.9	3/50	6.0	2.66 (0.83–8.54)	2.04 (0.55–8.32)
Low birthweight	42/48	87.5	29/50	58	1.39 (1.06–1.83)	1.23 (0.85–2.55)
Very low birthweight	25/48	52.1	7/50	14.0	3.31 (1.58–6.91)	2.22 (1.07–5.73)
Respiratory distress syndrome	15/48	31.3	3/50	6.0	5.07 (1.75–14.70)	3.88 (1.09–21.03)
Intraventricular hemorrhage	3/48	6.3	3/50	6.0	1.13 (0.27–4.74)	1.09 (0.21–4.98)
Sepsis	0/48	0	2/50	4.0	0.23 (0.01–4.58)	0.18 (0.01–5.68)
NICU	5/22	22.7	11/20	55.0	0.35 (0.06–2.12)	0.45 (0.12–2.49)

Logistic regression was performed to correct data for confounders (previous PTB, gestational age at randomization). Primary outcome was PTB < 34 weeks of gestation.

aOR, adjusted odds ratio; N/A: not applicable; NICU: neonatal intensive care unit admission; PTB, preterm birth; RR, relative risk.

Table 3. Primary outcome in subgroup analyses.

		Cerclage		Control			
Population	Outcome	*n*	%	*n*	%	RR (95% CI)	aOR (95% CI)
Prior PTB < 37 weeks	PTB < 34 weeks	4/6	66.7	1/1	100	0.86 (0.32–2.27)	–
Without previous PTB	PTB < 34 weeks	11/18	61.1	5/24	20.8	2.29 (0.35–4.94)	–
Prior STL 16–23 weeks	PTB < 34 weeks	2/3	66.7	0/0		N/A	–
Cone biopsy	PTB < 34 weeks	1/2	50.0	1/4	25.0	2.00 (0.22–17.89)	–
GA with short CL < 20 weeks	PTB < 34 weeks	6/7	85.7	0/1	0	3.25 (0.29–36.67)	–
GA with short CL ≥ 20 weeks	PTB < 34 weeks	9/17	52.9	6/24	25.0	2.12 (0.93–4.83)	–
CL ≤ 15 mm	PTB < 34 weeks	6/7	85.7	1/6	16.7	1.74 (1.14–21.57)	1.44 (0.7–8.46)

Logistic regression was performed to correct data for confounders (previous PTB, GA at randomization).
aOR, adjusted odds ratio; CL, cervical length; GA, gestational age; N/A, not applicable; PTB, preterm birth; RR, relative risk, random effect model; STL, second-trimester loss.

differences between singleton pregnancies with or without previous PTB (6). For twins, we reported only the rates of PTB < 35 weeks and perinatal mortality, without looking at any patient characteristic, risk factor, or other outcome measures (6). Both the American Congress of Obstetricians and Gynecologists and the Society of Maternal and Fetal Medicine have reported on the subgroup analysis data of that original meta-analysis on the increased rate of PTB at <35 weeks of gestation in twins with TVU CL < 25 mm who received cerclage compared with controls (29,30). Since then, several colleagues have asked for more details regarding these data, in particular regarding assessing possible confounders in demographic characteristics, risk factors and subgroups for effects on the incidence of PTB in the cerclage compared with the control groups just for twin gestations. As no new RCT has been published since then regarding this issue, these data remain the only available Level 1 data on the issue of cerclage effectiveness in twin gestations with short CL.

This new, much more detailed meta-analysis solely on the twin data seems to point mostly to no effect of cerclage, rather than to a detrimental effect. The outcomes are now reported not only adjusted by confounders, but also by a random-effects model rather than a fixed one. A random effects model is now chosen due to the differences between the studies, and because it has the advantages of more degrees of freedom providing greater generalizability of the results (31). That is why the RR for PTB < 35 weeks is now 1.63 (95% CI 0.88–3.02) with a random effects model (Table 2), as was used in the related Cochrane Review (32), instead of 2.15 (95% CI 1.15–4.01) with a fixed effects model, as reported in 2005 (6).

The recent Cochrane meta-analysis of cerclage in twins showed that placing a circumferential cervical stitch is not associated with benefits and indeed is associated with a worse neonatal outcome (32). This meta-analysis did not evaluate any demographic characteristics or risk factors, and therefore we did not perform any logistic regression to correct data for any variables that were significantly different between groups. Another meta-analysis evaluated use of cerclage for preventing PTB in twin pregnancies (33). This meta-analysis included all RCTs comparing the effects of cervical cerclage with controls, including not only women with ultrasound-indicated cerclage, but also history-indicated cerclage and physical examination-indicated cerclage, incorporating all the data in a single analysis. This type of analysis makes clinical use of such data limited.

Only two non-randomized controlled studies have been published regarding the efficacy of cerclage compared with no cerclage in twin gestations with second trimester short maternal TVU CL (34,35). Both reported no significant effect, neither of benefit or detrimental, on PTB outcomes. One of the strengths of our study is inclusion of only RCT data on ultrasound-indicated cerclage in twins. Most of the studies analyzed had a low risk of bias as measured by the Cochrane Collaboration's tools (9). We also used patient-level data. Risk of publication bias was assessed by visual inspection of the Forest plot (Figure 3), and the symmetric plot suggested no publication bias.

Limitations of our study are inherent to those of the included RCTs, which overall were, however, of good quality and with low risk of bias. Another limitation is the small number of twin gestations randomized. All studies included in our meta-analysis evaluated the efficacy of cerclage not only for twins but also for singleton pregnancies, but ultrasound-indicated cerclage in twins has not been studied in a dedicated RCT (19–21). The only small randomized trial of cerclage on twins evaluated history-indicated cerclage, and did not show any effect of cerclage on PTB (18). As the three included trials did not stratify their randomization sequences for twins, the two groups were dissimilar in incidence with regard to previous PTB and gestational age at randomization.

Conclusion

Based on these Level 1 data, cervical cerclage cannot currently be recommended for clinical use in twin pregnancies where the mother has a short CL on TVU in the second trimester.

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